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The stereochemistry of 1,3-dipolar cycloaddition of internally H-bonded chiral methylenenitrones

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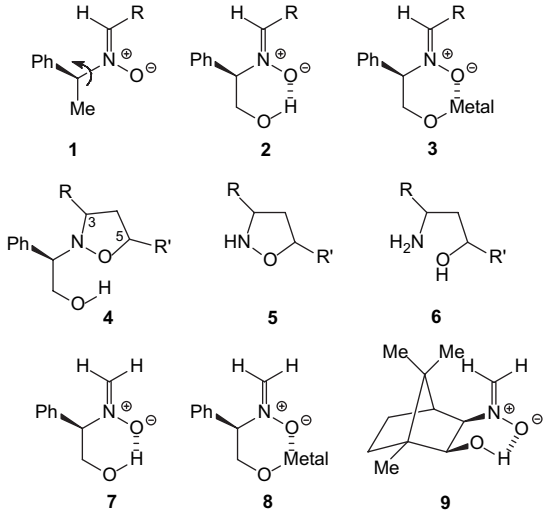
Abstract—A study of diastereoselectivity in the cycloaddition reactions of a series of mono- and disubstituted alkenes with two chiral, internally H-bonded methylenenitrones has been carried out. The high degree of stereochemical control in the presence of anhydrous magnesium bromide has been explained in terms of a metal chelated transition state. Intramolecular cycloaddition involving a methylenenitrone containing an alkene moiety linked to a nitrogen gave a stereoselective addition product.

1. Introduction

Among a plethora of functional groups, the nitrone functionality has etched a place of distinction in organic synthesis. Remarkable regio-, stereo-, face-, and chemoselectivity along with efficient incorporation of multiple stereocenters have made nitrone cycloaddition reactions an attractive and efficient key step in the synthesis of a great many natural products of biological interest.[1] In recent years, focus has been shifted toward asymmetric nitrone cycloaddition reactions; enantioselective,[2] catalytic enantioselective,[3] and diastereoselective[4] synthetic methodologies, as well as metal-assisted stereocontrol[5] have been reported. The efficacy of a diastereoselective approach using a chiral nitrone very much depends on the ability of the chiral auxiliary to effectively transfer chirality to the newly created stereocenters. The poor selectivity observed[6] in the cycloaddition reactions of the chiral nitrone **1** may be attributed to its conformational flexibility by virtue of easy N–C bond rotation (Scheme 1). However, intramolecularly H-bonded nitrone **2**, or its tightly metal-chelated form **3**, severely restricts the bond rotation, thereby allowing the incoming alkenes to experience two different faces of the nitrone. Approach of the alkenes toward the less hindered face of the nitrone increases the diastereoselectivity.[7,8] The chiral auxiliary in **2** is receiving increasing attention owing to its easy reductive cleavage from the cycloadduct **4**, so as to provide a simple and efficient access to **5** to synthetically important 1,3-aminoalcohols **6**.



Scheme 1.

Even though the nitrone cycloaddition reactions of *C*,*N*-disubstituted nitrones have been studied in great detail,[1] the chemistry of chiral (or even achiral) *N*-substituted nitrones (i.e., methylenenitrones) has only been investigated to a limited extent.[7,9] Here we report a systematic study detailing the regio- and stereochemical features associated with the cycloaddition of the chiral internally H-bonded methylenenitrones **7** and **9** onto a series of mono- and 1,1-disubstituted alkenes. The study would indeed provide a composite picture that reflects the scope and limitations associated with the addition reactions of the methylenenitrones. In order to make the nitrones more versatile, we would also like to explore an intramolecular nitrone cycloaddition reaction involving an *N*-alkenylnitrone that may be obtained by linking

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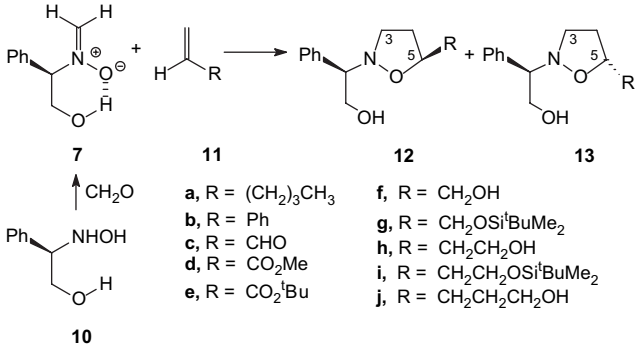
an alkene moiety to the oxygen atom of the hydroxyl group in the nitrone **7**.

2. Results and discussion

The stereochemical details of the addition of the nitrone **7** onto several monosubstituted alkenes (Scheme 2) along with the reaction temperatures, solvent, isolated yield, and composition of diasteroemeric cycloadducts are given in Table 1.



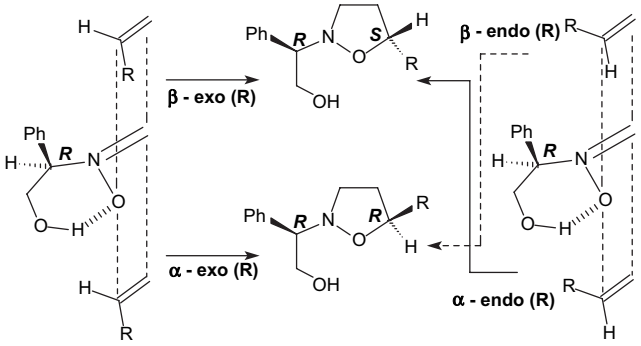
Scheme 2.

Reaction of nitrone **7** with 1-hexene gave a mixture of diastereomers **12a** and **13a** in a ratio of 77:23, while the ratio was improved to 85:15 in the presence of anhydrous $MgBr_2$. The nitrone **7** is expected to be internally H-bonded as shown in Scheme 1. This would place the phenyl group on the β-face of the nitrone, while the H on the stereocentre remains on the α-face (Scheme 3). While both the '*α-exo* (R) approach' (i.e., the approach of the alkene with *exo*-oriented R group toward the α-face of the nitrone) and '*β-endo* (R) approach' of the alkene would lead to the same diastereomer with '*RR*' configuration, the '*α-endo* (R)' and '*β-exo* (R)' approaches give the other diastereomer having '*RS*' configuration. The face selectivity in the addition reaction of methylenenitrones, like **7**, cannot be determined since, for instance, the formation of the '*RR*' diastereomer is the combined outcome of approach of the alkene to both faces of the nitrone. Likewise, the stereoselectivity in each face (*exo*/*endo* ratio) cannot be determined, since each diastereomer can be obtained by both the *exo* and *endo* mode of attack. This problem does not arise in the case of C-substituted chiral nitrones, since their addition reactions would create three chiral centers, and as such, each of the approaches would generate a different diastereomer, thus allowing the determination of face selectivity as well as stereoselectivity of each face. For the current nitrone **7**, it can be presumed that the α-face of the nitrone will be preferentially attacked, and the steric interactions would then dictate the *exo* mode of approach. In line with this reasoning, the 1-hexene cycloaddition resulted in the formation of the major adduct **12a** predominantly via '*α-exo* (R) approach'. In the presence of $MgBr_2$, the metal chelation imparts better stability to the face than the H-bonded form, thereby leading to a better face selectivity.

Table 1. Regio- and stereochemistry of the cycloaddition of the nitrone **7** with monosubstituted alkenes **11**

Alkene **11**	Temp (°C)	Time (h)	Solvent	Lewis acid[a]	Isolated yields (%)	Diastereomeric ratio (**12**:**13**)
a	105	8	Toluene	None	90	77:23
	65	48	CH_2Cl_2	$MgBr_2$	77	85:15
b	0	144	$CHCl_3$	None	65	78:22
	25	72	$CHCl_3$	None	75	76:24
	50	6	$CHCl_3$	None	90	73:27
	75	24	$CHCl_3$	$BF_3{\cdot}OEt_2$	75	79:21
	65	24	CH_2Cl_2	$MgBr_2$	92	86:14
c	65	6	$CHCl_3$	None	65	44:56
d	0	144	$CHCl_3$	None	64	44:56
	25	72	$CHCl_3$	None	74	48:52
	50	6	$CHCl_3$	none	86	46:54
	65	24	$CHCl_3$	$BF_3{\cdot}OEt_2$	85	38:62
	65	6	$CHCl_3$	$Ti(O^iPr)_4$	83	62:38
e	65	6	$CHCl_3$		85	56:44
f	85	6	Toluene	None	83	62:38
	40	24	CH_2Cl_2	$MgBr_2$	90	4:96[b]
g	105	12	Toluene	None	88	75:25
h	105	8	Toluene	None	93	70:30
	65	48	CH_2Cl_2	$MgBr_2$	91	89:11
i	105	12	Toluene	None	90	82:18
j	105	8	Toluene	None	92	73:27
	65	48	CH_2Cl_2	$MgBr_2$	93	91:9

[a] In the presence of 1 equiv of Lewis acid as described in Section 3.3.
[b] Work taken from Ref. 7.



Scheme 3.

Styrene undergoes addition to give **12b** and **13b** in a ratio of 73:27 at 50 °C. At lower reaction temperatures of 25 and 0 °C, the ratio is changed slightly in favor of the major isomer; decreasing temperature is expected to make the H-bonding more effective in arresting conformational change to the open form by C–N bond rotation. However, there was only a slight improvement in the diastereoselectivity. The diastereoselectivity is further improved in the presence of Lewis acids. Based on the earlier discussion, the major adduct is obtained via '*α-exo* (R) approach'; steric factor of the phenyl group in styrene is known[10] to overwhelm any possible secondary orbital interactions in an *endo* approach.

The reaction of nitrone **7** with acrolein and methyl acrylate gave a diastereomeric mixture of **12c**, **13c** and **12d**, **13d**, respectively; in each case a slight excess of the *endo* adduct **13** is obtained via '*α-endo* (R) approach'. While the cycloaddition favors the formation of **13d** in the presence of $BF_3{\cdot}OEt_2$, the stereoselectivity is reversed with $Ti(O^iPr)_4$.

The addition of the nitrone **7** with *tert*-butyl acrylate gave the diastereomers **12e** and **13e** in a 56:44 ratio; a slight excess of the *exo* adduct **12e** demonstrates the steric hindrance of the *tert*-butyl group. To confirm the stereochemistry, adduct **13d** was subjected to X-ray crystallographic analysis; the ORTEP representation is shown in Figure 1. Complete stereochemical analysis was carried out by conversion of the *tert*-butyl acrylate adducts **12e**, **13e** into methyl acrylate adducts **12d**, **13d** by ester exchange with methanol/HCl. The stereochemistry of the acrolein adducts **12c**, **13c** was correlated with that of the methyl acrylate adducts **12d**, **13d** by their conversions to the alcohol adducts **12f** and **13f**.

Addition reactions of nitrone **7** with allyl alcohol (**11f**), 3-buten-1-ol (**11h**), and 4-penten-1-ol (**11j**) afforded **12f**, **12h**, and **12j**, respectively, as the major adducts via 'α-*exo* (R) approach' (Scheme 3). Among these three alcohols, allyl alcohol gave the largest proportion of α-*endo* (R) adduct **13f**. The higher tendency of the allyl moiety than 3-butenyl for the *endo* approach is also demonstrated in the addition reactions of *tert*-butyldimethylsilyl allyl ether **11g** and *tert*-butyldimethylsilyl 3-butenyl ether **11i**; the adduct ratio changes from 75:25 for **12g/13g** to 82:18 for **12i/13i**. Significant preference for the *endo* approach observed in the addition of allyl ether and alcohols may be attributed to the stabilizing interaction between the nitrogen atom of the nitrone LUMO with the oxygen lone pair of the alkene (Fig. 2).[10,11]

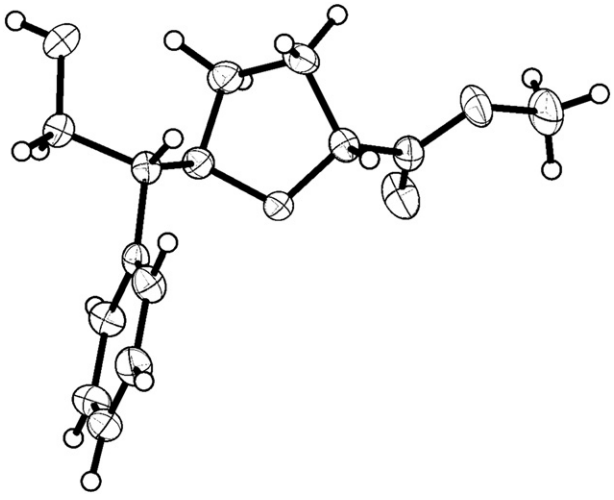


Figure 1. ORTEP drawing of **13d**.

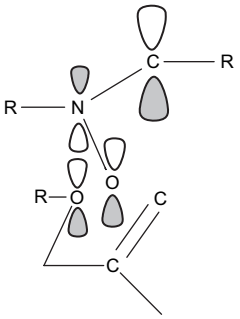


Figure 2. Stabilizing interaction between nitrogen in nitrone LUMO and oxygen lone pair of the alkene.

Allyl alcohol (**11f**), 3-buten-1-ol (**11h**), and 4-penten-1-ol (**11j**) appear to undergo cycloadditions in the presence of $MgBr_2$ with much higher diastereoselection to give **12f/13f**, **12h/13h**, **12j/13j**, respectively, in a ratio of 4:96,[7] 89:11, and 91:9. It is interesting to note the change in stereoselection in this series of alkenes differing in the length separating the OH and alkene functionality. The configuration of the overwhelmingly predominant adduct **13f** is consistent with a magnesium-chelated *endo* approach of the CH_2OH group of the allyl alcohol from the less hindered face of the nitrone[7,8] as depicted in **A** (Fig. 3). However, the transition state, for the higher homologs of allyl alcohol, as depicted in **B** is expected to give cycloadducts (**12h** or **12j**) via *exo*-mode of attack by the alkene. This was indeed observed experimentally; the study thus provided information on the effect of the intervening length between the alkene and hydroxyl moiety on the stereoselection.

Next, we pursued the cycloaddition of nitrone **7** with a number of 1,1-disubstituted alkenes **14** (Scheme 4). The results of our stereochemical analysis are summarized in Table 2. The addition of methacrolein **14a** to the nitrone **7** gave the hemiacetals **15a′** and **16a′** instead of the expected adducts **15a** and **16a** (in the aldehyde form). We were able to isolate one of the hemiacetals—presumably the **15a′**—in pure form. The configuration of adducts was correlated to the methallyl alcohol adducts **15d** and **16d** by $NaBH_4$ reduction of the crude cycloaddition products. The ratio of the isomers **15a** and **16a** was determined to be 66:34, respectively. For the favorable secondary orbital interactions, the aldehyde group is assumed to have the *endo* orientation in **15a**, formed via 'α-*endo* (CHO) approach'.

The cycloaddition of **7** with methyl methacrylate **14b** at 50 °C gave a separable mixture of **15b** and **16b** in a ratio of 86:14. The favorable secondary orbital interactions place the ester in the *endo* orientation in **15b**. The cycloaddition at 0 and 25 °C gave the adducts **15b** and **16b** in a ratio of 90:10 and 87:13, respectively. The ratio is slightly changed at lower temperatures in favor of the major isomer, presumably as a result of more effective H-bonding in reducing conformational change to the open form by C–N bond rotation. The stereochemistry of adducts was correlated to the methallyl alcohol adducts **15d** and **16d** by lithium aluminum hydride reduction of the crude cycloaddition products. Addition of nitrone **7** with *tert*-butyl methacrylate **14c** gave a non-separable mixture of cycloadducts **15c** and **16c** in a ratio of 87:13. The adducts **15c** and **16c** were converted into the methyl methacrylate adducts **15b** and **16b** by ester exchange with methanol. The addition reaction of nitrone **7** onto

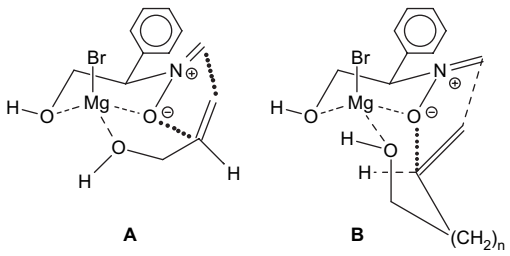
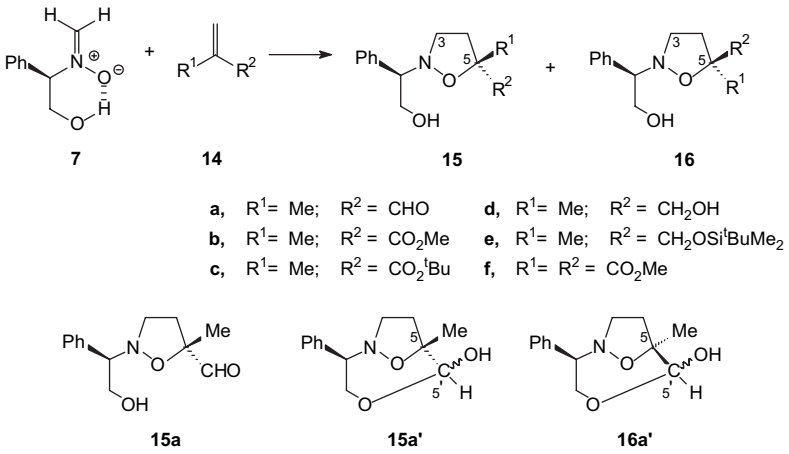


Figure 3. Metal chelated transition states for the cycloaddition reactions.



Scheme 4.

Table 2. Stereochemistry of cycloaddition[a] of the nitrone **7** with 1,1-disubstituted alkenes **14**

Alkene **14**	Temp (°C)	Solvent	Lewis acid	Isolated yields (%)	Diastereomeric ratio (**15**:**16**)
a	65	$CHCl_3$	None	93	66:34
b	0	$CHCl_3$	None	53	90:10
	25	$CHCl_3$	None	87	87:13
	50	$CHCl_3$	None	80	86:14
	65	$CHCl_3$	$BF_3{\cdot}OEt_2$	84	86:14
c	65	$CHCl_3$	None	85	87:13
d	90	Toluene	None	82	67:33
	65	CH_2Cl_2	$MgBr_2$	95	97:3
e	110	Toluene	None	74	58:42
f	50	$CHCl_3$	None	90	100

[a] Duration of reaction: 6 h in the absence of Lewis acid (except for **14e** the reaction was run for 12 h), and 24 h in the presence of Lewis acid.

conjugated 1,1-disubstituted alkenes **14** gave better stereoselectivity than their monosubstituted counterparts **11** as a result of a marked preference for the '*α-endo* (–C═O) approach'. While for the stereoselection in monosubstituted alkenes, the steric factor (H vs R) and secondary orbital interactions operate in opposite directions, the secondary orbital interaction is the dominant player in **14** since the steric differences between 'Me' and '–C═O' are very minimal.

Reaction of nitrone **7** with methallyl alcohol **14d** gave a non-separable mixture of cycloadducts **15d** and **16d** in a ratio of 67:33. Significant change in the stereoselection was observed when this addition reaction was carried out in the presence of anhydrous $MgBr_2$; the isomers **15d** and **16d** were obtained in a 97:3 ratio. The configuration of the major adduct is based on a transition state similar to that depicted in **A** (Fig. 3); overwhelming preference of the CH_2OH group to assume *endo* orientation is manifested. The addition of silylether alkene **14e** afforded cycloadducts **15e** and **16e** in a 58:42 ratio; the stereochemistry of the cycloadducts was correlated to the methallyl alcohol adducts **15d** and **16d** by their conversion into the corresponding alcohols. As discussed before, significant preference for the *endo*-approach of the CH_2O– moieties is attributed to the stabilizing interaction as depicted in Figure 2. Reaction of nitrone **7** with dimethyl methylenemalonate **14f** gave the cycloadduct **15f** as the sole regiomer in an excellent yield.

The results discussed above are in general agreement with the Frontier orbital treatment of the nitrone 1,3-dipolar cycloadditions.[12] In the case of mono- as well as 1,1-disubstituted alkenes, the nitrone (HOMO)–alkene (LUMO) contribution does not offer any regiochemical preference, since the nitrone HOMO has a similar magnitude of orbital coefficients at both the nitrogen and carbon terminals. However, the nitrone (LUMO)–alkene (HOMO) prefers the formation of 5-substituted regioisomers by uniting the larger terminal coefficients in the transition state (Fig. 4).[13]

Next, we studied the cycloaddition behavior of another internally H-bonded chiral methylenenitrone **9** with several mono- (**11**) and di-substituted alkenes (**14**) (Scheme 5). The stereochemical analyses of these additions are summarized in Table 3. Cycloaddition of 1-hexene (**11a**) with nitrone **9** gave a mixture of the cycloadducts **18** and **19** in a ratio of 95:5. The reaction of nitrone **9** with styrene (**11b**) afforded a non-separable mixture of adducts **20** and **21** in a ratio of 96:4. The major isomer in each case is assigned the configuration with an *exo*-oriented *n*-butyl/or

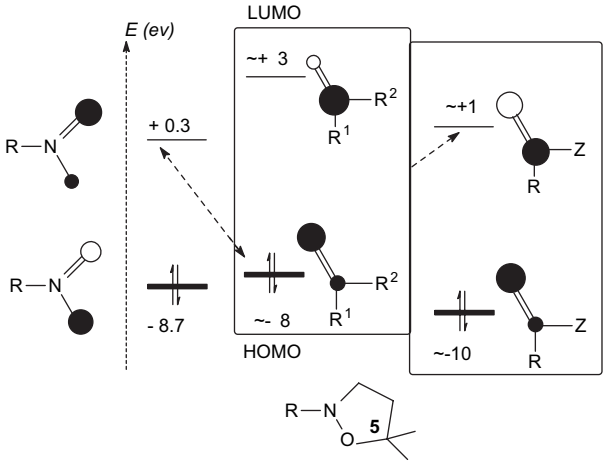
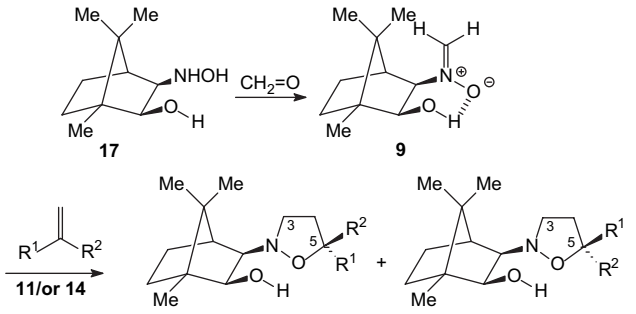


Figure 4. A qualitative representation of the energies and orbital coefficients of methylenenitrone and alkene Frontier orbital energies of nitrone and mono- and 1,1-disubstituted alkenes.

phenyl as expected via a sterically favored transition state with an *exo*-disposition of the alkene substituent. The addition of methyl acrylate (**11d**) to the nitrone **9** gave **22** and **23** in a ratio of 65:35. The stereochemistry of the major adduct **22** was confirmed by X-ray crystallographic analysis; the ORTEP representation is shown in Figure 5. The reaction of the nitrone **9** with methyl methacrylate (**14b**) afforded a mixture of adducts **24** and **25** in a ratio of 66:34. Addition of the nitrone **9** with dimethyl methylenemalonate **14f** gave cycloadduct **26** as the sole regiomer as expected.



Scheme 5.

The results indicate that the additions of nitrone **9** onto normal monosubstituted alkenes are more diastereoselective than the additions of the nitrone **7**. For example, while the addition of nitrone **7** to 1-hexene (**11a**) and styrene (**11b**) gave the diastereomers **12** and **13** in a ratio of 3.35:1 and 2.70:1, respectively, the corresponding ratio for the addition of nitrone **9** leading to the diastereomers **18/19** and **20/21** became 24:1 and 19:1, respectively. In an H-bonded form, the

Table 3. Regio- and stereochemistry of the cycloaddition[a] of the nitrone **9** with mono- **11** and di-substituted alkenes **14**

Alkene **11/14**	Temp (°C)	Solvent	Isolated yields (%)	Diastereomeric ratio
11a	107	Toluene	79	(**18/19**) 95:5
11b	65	$CHCl_3$	81	(**20/21**) 96:4
11d	55	$CHCl_3$	85	(**22/23**) 65:35
14b	50	$CHCl_3$	88	(**24/25**) 66:34
14f	50	$CHCl_3$	79	(**26**) —

[a] Duration of reaction: 8 h.

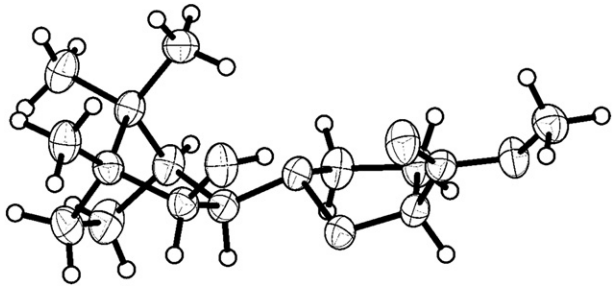
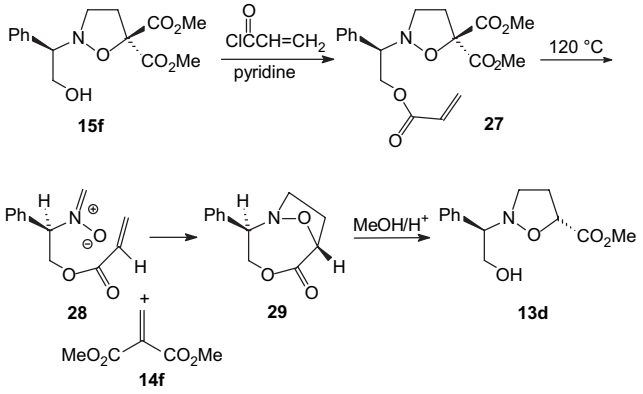


Figure 5. ORTEP drawing of **22**.

β face of nitrone **9** is indeed very crowded thereby leading to the preferential attack on the α face with *exo*-disposition of the alkene substituents. A similar trend is observed in the addition of methyl acrylate (**11d**); while nitrone **7** afforded **12d** and **13d** in a 0.9:1 ratio; the corresponding ratio for the reaction of nitrone **9** to give **22** and **23** was found to be 1.9:1. The results reemphasize the dominance of steric factor over secondary orbital interactions in the additions of the nitrone **9**.

Finally, we studied the intramolecular nitrone–alkene cycloaddition reaction involving chiral nitrone **28** having an alkene moiety linked to the nitrogen atom (Scheme 6). While intramolecular cycloadditions of *C*-alkenylnitrones, having an alkene moiety attached to the C-terminal, have been widely studied, the addition reaction of the *N*-alkenylnitrone is very limited.[4c] The synthesis of nitrone **28** is not so straightforward; instead we pursued a protection–deprotection chemistry of the nitrone functionality. Adducts derived from the addition reaction of a highly polarized alkene like dimethylmethylene malonate are known to undergo facile cycloreversion.[10] The cycloadduct **15f** was converted into its acrylate ester **27**. It is gratifying to see the adduct **27** undergo cycloreversion, followed by intramolecular cycloaddition of the intervening alkenenitrone **28**, to give the single bicyclic adduct **29**. The configuration of adduct is corroborated by spectral analyses including COSY NMR and also by conversion into the known methyl acrylate adduct **13d**. Inspection of the molecular models indicates the favorable transition state involving the alkene in an '*endo* (R)-approach'.



Scheme 6.

A systematic study of asymmetric reactions of two chiral methylenenitrones with several mono- and di-substituted alkenes has been carried out. The diastereoselection observed in our study reflects the scope and limitation inherent in these important cycloaddition reactions. Remarkable stereoselectivity observed in the intramolecular reaction (**28**→**29**) paves the way to explore reactions involving nitrone–alkenes differing in structure and intervening spacer length between the nitrogen and the alkene moieties.

3. Experimental

3.1. General

Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. All mps are uncorrected. IR

spectra were recorded on a Perkin–Elmer 16F PC FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde, 1-hexene, styrene, allyl alcohol, 3-buten-1-ol, 4-penten-1-ol methyl acrylate, methyl methacrylate, methylallyl alcohol, *m*-chloroperbenzoic acid (70% purity), D(−)-α-phenylglycinol (i.e., (*R*)-phenylglycinol), hydroxylamine hydrochloride from Fluka were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. $MgBr_2$ was prepared freshly by reaction of Mg with 1,2-dibromoethane. Alkanols were silylated using ^{t}BuMe$_2$SiCl in the presence of imidazole in DMF. All reactions were carried out under N_2.

The chiral hydroxylamine (*R*)-3-hydroxyamino-2-phenylethanol (**10**) was prepared in 80% yield according to the literature procedures;[14,15] mp 68–68.5 °C (methanol/ether); $[\alpha]_D^{23}$ −62 (*c* 2.00, methanol). The chiral 3-(hydroxyamino)-borneol (**17**) was prepared as described.[16,17]

3.2. General procedure for the cycloaddition reactions

In all the cycloadditions involving electron deficient conjugated alkenes, a mixture of the hydroxylamine **10** (5 mmol), paraformaldehyde (7.5 mmol), and a solvent (15 cm^3) was stirred in a closed flask at 50 °C for 4 h to generate the nitrone **7**. The nitrone solution was then treated with $MgSO_4$ (1 g) and the alkene. The conjugated alkene was not added prior to the formation of the nitrone in order to avoid any Michael addition of the hydroxylamine. For the additions involving normal alkenes, all the reactants were added in the beginning, and the reaction mixture was directly heated at the specified temperatures (Tables 1–3). The alkenes used, with the amounts in mmol given in parentheses, were as follows: 1-hexene (30), styrene (20), acrolein (12), methyl acrylate (15), *tert*-butyl acrylate (10), allyl alcohol (25), *tert*-butyldimethylsilyl allyl ether **11g** (8), 3-buten-1-ol (15), *tert*-butyldimethylsilyl 3-butenyl ether **11i** (8), 4-penten-1-ol (12), methyl methacrolein (8), methyl methacrylate (15), *tert*-butyl methacrylate (10), methallyl alcohol (20), *tert*-butyldimethylsilyl 2-methyl-2-propenyl ether **14e** (10), and dimethyl methylenemalonate **14f** (6). The reaction temperatures, time, solvent used, composition of adducts, and isolated yields are given in Tables 1 and 2. The reaction mixture was filtered, evaporated to remove the solvent and excess alkene (if volatile) to give crude residues containing the cycloadducts, which were then purified and analyzed.

The nitrone (**9**)–alkene (**11**/**14**) reactions were carried out in a similar way as described above using the hydroxylamine **17** instead of **10**. The reaction temperatures, time, solvent used, composition of adducts, and isolated yields are given in Table 3.

3.2.1. Cycloaddition of nitrone 7 with 1-hexene (11a). The crude mixture of cycloadducts was purified by chromatography over silica using ether/hexane mixture as eluant to give a non-separable mixture of isomers **12a** and **13a** as a colorless liquid (1.13 g, 90%) in a ratio of 77:23, respectively, as determined by integration and peak heights of several ^{1}H signals. (Found: C, 72.0; H, 9.2; N, 5.6. $C_{15}H_{23}NO_2$ requires C, 72.25; H, 9.30; N, 5.62%.) ν_{max} (neat) 3420, 2929, 2864, 1456, 1378, 1048, 852, 758 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.91 (3H, t, *J* 6.8 Hz), 1.00–1.90 (7H, m), 2.31 (1H, m), 2.75 (1H, m), 2.98 (1H, m), 3.45 (1H, m), 3.71 (1H, dd, *J* 3.3, 11.6 Hz), 3.85 (1H, dd, *J* 3.3, 7.7 Hz), 4.09 (1H, dd, *J* 7.7, 11.6 Hz), 4.29 (1H, m), 7.30 (5H, m). Non-overlapping signals of the minor isomer **13a** were displayed at δ 2.47 (1H, m), 3.75 (1H, dd, *J* 3.3, 7.7 Hz).

3.2.2. Cycloaddition of nitrone 7 with styrene (11b). The crude mixture of cycloadducts was purified by chromatography over silica using ether/hexane as eluant to give a non-separable mixture of the cycloadducts **12b** and **13b** (1.21 g, 90%) as a colorless liquid in a ratio of 73:27 as determined by integration of the C5(H) signals. (Found: C, 75.6; H, 6.9; N, 5.1. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%.) ν_{max} (neat) 3417, 3061, 3029, 2881,1603, 1493, 1454, 1360, 1310, 1179, 1028, 950, 913, 847, 760, and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) broad NMR signal between δ 2.2–5.5 ppm due to relatively slow nitrogen inversion. The proton signals for the individual isomers, as detailed below, are extracted from the spectrum of the non-separable mixture.

Major isomer **12b**: δ_H ($CDCl_3$, −40 °C) 2.20 (1H, m), 2.77 (1H, m), 2.98 (1H, m), 3.28 (1H, m), 3.70 (1H, OH), 3.76 (1H, m), 4.05 (1H, m), 4.22 (1H, m), 5.39 (1H, dd, *J* 6.6, 8.1 Hz), 7.40 (10H, m). C5(H) signal for minor invertomer appear at 4.97 ppm (t, *J* 7.5 Hz) in a ratio of 95:5; δ_C ($CDCl_3$, −40 °C) 38.74, 53.94, 68.73, 70.83, 78.93, 128.8 and 129.8, 137.68 and 140.59. (TMS: 0.0; $CDCl_3$ middle carbon: 77.1). The spectrum also revealed the presence of weak signals for the minor invertomer.

Minor isomer **13b**: δ_H ($CDCl_3$, −40 °C) 2.10 (1H, m), 2.60 (1H, m), 2.65 (1H, m), 3.15 (1H, m), 3.55 (1H, m), 3.70 (1H, OH), 4.00 (1H, m), 4.17 (1H, m), 5.16 (1H, dd, *J* 6.9, 8.1 Hz), 7.4 (10H, m). C5(H) signal for minor invertomer of minor isomer appear at 4.72 ppm (t, *J* 7.1 Hz) in a ratio of 92:8; δ_C ($CDCl_3$, −40 °C) 36.26, 55.07, 68.42, 74.17, 80.22, and overlapping signals of aromatic carbons (TMS: 0.0; $CDCl_3$ middle carbon: 77.1). In addition to these signals, signals for the minor invertomer can also be seen in the spectrum.

The above cycloaddition reaction was repeated at 0 and 25 °C using the hydroxylamine **10** (38 mg, 0.25 mmol). The yields and ratio of the diastereomers are given in the Table 1.

3.2.3. Cycloaddition of nitrone 7 with acrolein (11c), and sodium borohydride reduction of cycloadducts 12c and 13c to 12f and 13f. The crude mixture of cycloadducts **12c** and **13c** in methanol (5 cm^3) was treated with $NaBH_4$ (150 mg) and stirred at 20 °C for 1 h. After removal of the solvent by a gentle stream of N_2, the reaction mixture was taken up in a saturated K_2CO_3 solution (7 cm^3), and extracted with CH_2Cl_2 (3×10 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated and the residual liquid was purified by silica gel chromatography using ether/methanol (95:5) as the eluant to give a non-separable mixture **12f** and **13f** (65%) in a ratio of 44:56, respectively,

as determined by integration of non-overlapping proton signals (vide infra: Section 3.2.4) at δ 2.08 (1H, m), 2.31 (1H, m) for the major isomer **13f**, and at δ 2.14 (2H, m) for minor isomer **12f**.

3.2.4. Cycloaddition of nitrone 7 with methyl acrylate (11d), and lithium aluminum hydride reduction of cycloadducts 12d and 13d to 12f and 13f. The crude mixture of cycloadducts was chromatographed over silica using ether/hexane as eluant to give the minor isomer **12d** (476 mg, 38%) as a colorless liquid. Continued elution afforded a mixture of **12d** and **13d** (239 mg, 19%) and finally the major isomer **13d** (369 mg, 29%) as colorless needles. The diastereomeric ratio of **12d** and **13d** was found to be around 46:54, respectively, as determined by integration of several proton signals in ^{1}H NMR spectrum of the crude reaction mixture. The stereochemistry of the major isomer **13d** was assigned by X-ray diffraction analysis.

Compound **12d**: (Found: C, 61.9; H, 6.9; N, 5.5. $C_{13}H_{17}NO_4$ requires C, 62.14; H, 6.82; N, 5.57%.) ν_{max} (neat) 3491, 3061, 3029, 2952, 2850, 1740, 1603, 1493, 1406, 1350, 1290, 1211, 1083, 937, 826, 760, and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.41 (1H, m), 2.55 (1H, m), 2.99 (1H, m), 3.28 (1H, m), 3.76 (1H, m), 3.79 (3H, s), 3.95 (2H, m), 4.67 (1H, m), 7.33 (5H, m).

Compound **13d**: mp 63–63.5 °C (CH_2Cl_2/hexane). (Found: C, 62.0; H, 6.7; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.14; H, 6.82; N, 5.57%.) ν_{max} (KBr) 3481, 3088, 3063, 3024, 2982, 2942, 2904, 2876, 1740, 1496, 1452, 1433, 1364, 1316, 1299, 1279, 1209, 1172, 1111, 1081, 1057, 1023, 948, 915, 864, and 758 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.41 (1H, m), 2.43 (1H, m), 2.91 (2H, m), 3.30 (1H, br, OH), 3.75 (1H, m), 3.80 (3H, s), 3.96 (1H, dd, *J* 4.0, 7.6 Hz), 4.17 (1H, dd, *J* 7.6, 11.2), 4.56 (1H, m), 7.30 (5H, m).

The above cycloaddition reaction was repeated at 0 and 25 °C for a duration of 6 and 3 days, respectively, to afford the cycloadducts in 64 and 74% yields. The ratio of the **12d** and **13d** at 0 and 25 °C were found to be 44:56 and 48:52, respectively.

To a stirred solution of **12d** (100 mg, 0.40 mmol) in ether (15 cm^3) was added lithium aluminum hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g), and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 95:5 CH_2Cl_2/methanol as the eluant to give **12f** as a colorless liquid (85 mg, 95%). (Found: C, 64.4; H, 7.6; N, 6.3. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%.) ν_{max} (neat) 3300, 3060, 3026, 2920, 1602, 1492, 1453, 1270, 1188, 1034, 870, 846, 759 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.08 (1H, m), 2.31 (1H, m), 2.40–3.50 (5H, br), 3.64 (1H, m), 3.75 (2H, m), 4.09 (1H, m), 4.43 (1H, m), 7.35 (5H, m).

The above procedure was repeated with **13d** to give the corresponding **13f** (81 mg, 91%) as a colorless liquid. (Found: C, 64.5; H, 7.7; N, 6.1. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%.) ν_{max} (neat) 3300, 3031, 2922, 2862, 1449, 1035, 754 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.14 (2H, m), 2.25–3.50 (4H, br), 3.59–3.87 (4H, m), 4.10 (1H, m), 4.24 (1H, m), 7.31 (5H, m).

3.2.5. Cycloaddition of nitrone 7 with *tert*-butyl acrylate (11e), and conversion of cycloadducts 12e and 13e into methyl acrylate adducts 12d and 13d. The crude mixture of cycloadducts was purified by chromatography over silica using ether/hexane as eluant to give the non-separable adducts **12e** and **13e** as a colorless liquid in 85% yield. (Found: C, 65.4; H, 7.8; N, 4.6. $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77%.) ν_{max} (neat) 3470, 3060, 2976, 2929, 2876, 1732, 1602, 1454, 1368, 1292, 1234, 1157, 1077, 915, 843, 732 and 704 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.51 (9H, s), 2.30–2.50 (2H, m), 2.80–3.00 (1H, m), 3.20–3.60 (1H, br), 3.72–3.77 (1H, m), 3.94–4.20 (2H, m), 4.40–4.55 (1H, m), 7.32 (5H, m).

A mixture of the *tert*-butyl acrylate adducts **12e** and **13e** (50 mg, 0.153 mmol) in 5:1 methanol/HCl (1 cm^3) was stirred at 20 °C for 6 h. After removal of the methanol the residual liquid was taken up into CH_2Cl_2 (15 cm^3) and washed with 5% K_2CO_3 (5 cm^3). The organic layer was dried (Na_2SO_4) and concentrated to give a mixture of methyl acrylate adducts **12d** and **13d** as a colorless liquid. The ^{1}H NMR spectrum as analyzed before (Section 3.2.4) revealed isomers **12d** and **13d** in a ratio of 56:44, respectively.

3.2.6. Cycloaddition of nitrone 7 with allyl alcohol (11f). The crude mixture of cycloadducts was purified by chromatography over silica using ether/methanol (95:5) as eluant to give a non-separable mixture of the cycloadducts **12f** and **13f** (83%) as a colorless liquid. Major and minor isomers were found to be in a ratio of 62:38 as determined by integration of non-overlapping proton signals at δ 2.08 (1H, m), 2.31 (1H, m) for the major isomer, and at δ 2.14 (2H, m) for the minor isomer (IR and CHN analysis for **12/13f** are given in Section 3.2.4 vide supra).

3.2.7. Cycloaddition of nitrone 7 with *tert*-butyldimethylsilyl allylether (11g), and conversion of 12g and 13g to 12f and 13f. The crude mixture of cycloadducts was purified by chromatography over silica using 80:20 hexane/ether as eluant to give adduct **12g** (893 mg) as a colorless liquid, followed by a mixture of adducts **12g/13g** (298 mg). Continued elution afforded **13g** (296 mg,) as a colorless liquid. The overall isolated yield was thus determined to be 88%. Spectral analysis of the crude as well as the separated fractions revealed the presence of the **12g** and **13g** in a ratio of 75:25, respectively, as determined by the integration and peak heights of several proton signals (belonging to Si^{t}BuMe$_2$) of the crude as well as separated fractions.

Major isomer **12g**: (Found: C, 63.8; H, 9.3; N, 4.0. $C_{18}H_{31}NO_3Si$ requires C, 64.05; H, 9.26; N, 4.15%.) ν_{max} (neat) 3440, 3064, 3029, 2958, 2928, 2852, 1492, 1461, 1415, 1388, 1361, 1254, 1188, 1102, 939, 837, 778 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.093 (6H, s), 0.90 (9H, s), 1.92 (1H, m), 2.26 (1H, m), 2.68 (1H, m), 2.96 (1H, m), 3.11 (1H, m), 3.62 (1H, m), 3.70 (2H, m), 3.82 (1H, d, *J* 7.3 Hz), 4.10 (1H, dd, *J* 7.65, 11.6 Hz), 4.48 (1H, m), 7.30

(5H, m); δ_C ($CDCl_3$, +20 °C) (−)5.39 (2C), 18.22, 25.81 (3C), 29.86, 53.30, 64.71, 68.61, 71.63, 78.16, 128.00 (3C), 128.60 (2C), 138.32.

Minor isomer **13g**: (Found: C, 63.9; H, 9.4; N, 3.9. $C_{18}H_{31}NO_3Si$ requires C, 64.05; H, 9.26; N, 4.15%.) ν_{max} (neat) 3440, 3060, 3030, 2953, 2928, 2857, 1493, 1454, 1388, 1360, 1255, 1104, 1063, 1019, 938, 838, 778 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.092 (3H, s), 0.10 (3H, s), 0.92 (9H, s), 1.99 (1H, m), 2.15 (1H, m), 2.44 (1H, m), 2.96 (1H, m), 3.60–3.80 (5H, m), 4.10 (1H, dd, *J* 7.3, 11.3 Hz), 4.20 (1H, m), 7.30 (5H, m); δ_C ($CDCl_3$, +20 °C) (−)5.39 (2C), 18.22, 25.81 (3C), 29.86, 53.30, 64.71, 68.61, 71.63, 78.16, 128.00 (3C), 128.60 (2C), 138.32.

The separated adducts **12g** and **13g** were hydrolyzed to their corresponding alcohols **12f** and **13f**, respectively, in near quantitative yields. For instance, a solution of **12g** (100 mg) in MeOH/HCl (5:1) (1 cm^3) was stirred at 20 °C for 10 min. Removal of the solvent, basification (K_2CO_3), followed by extraction with CH_2Cl_2 afforded the hydrolyzed product **12f**.

3.2.8. Cycloaddition of nitrone 7 with 3-buten-1-ol (11h). The crude mixture of cycloadducts was purified by chromatography over silica using 95:5 ether/methanol as eluant to give a non-separable mixture of isomers **12h** and **13h** as a colorless liquid (1.10 g, 93%). Spectral analysis revealed the presence of **12h** and **13h** in a ratio of 70:30, respectively, as determined by integration of several ^1H signals. The C(5)H of **12h** and **13h** appeared at δ 4.51 and 4.23 ppm, respectively. One of the C(4)H of the major isomer **12h** appeared at δ 2.38 while the corresponding proton for the minor isomer **13h** appeared at 2.28 ppm. The following non-overlapping ^{13}C signals of the minor isomer was picked up from the spectrum of the mixture (vide infra: Section 3.2.9); δ_C ($CDCl_3$, +20 °C) 33.78, 37.72, 54.01, 60.10, 74.21.

3.2.9. Cycloaddition of nitrone 7 with *tert*-butyldimethylsilyl 3-butenyl ether (11i), and conversion of 12i into 12h. The crude mixture of cycloadducts was purified by chromatography over silica using 5:2 hexane/ether as eluant to give adduct **12i** (410 mg) as a colorless liquid, followed by a mixture of adducts **12i/13i** (1.17 g). The overall isolated yield was thus determined to be 90%. One of the C(4)H of the major isomer **12i** appeared at δ 2.36 while the corresponding proton for the minor isomer **13i** appeared at 2.19 ppm. The C(5)H of **12i** and **13i** appeared at δ 4.47 and 4.20 ppm, respectively. Spectral analysis of the crude as well as the separated fractions revealed the presence of the **12i** and **13i** in a ratio of 82:18, respectively.

Major isomer **12i:** (Found: C, 64.8; H, 9.3; N, 3.9. $C_{19}H_{33}NO_3Si$ requires C, 64.91; H, 9.46; N, 3.98%.) ν_{max} (neat) 3300, 3027, 2950, 2856, 1462, 1385, 1253, 1096, 930, 836, 777 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.07 (6H, s), 0.90 (9H, s), 1.55–2.0 (4H, m), 2.36 (1H, m), 2.73 (1H, m), 3.00 (1H, m), 3.7 (3H, m), 3.83 (1H, dd, *J* 3.1, 7.6 Hz), 4.09 (1H, dd, *J* 7.6, 11.6 Hz), 4.47 (1H, m), 7.32 (5H, m); δ_C ($CDCl_3$, −30 °C) (−) 5.50 (2C), 18.29, 25.81 (3C), 33.23, 37.61, 53.25, 59.92, 69.05, 70.88, 74.59, 127.78 (2C), 128.07, 128.69 (2C), 137.89.

The cycloadduct **12i** was hydrolyzed in methanolic HCl as before (Section 3.2.7) to obtain the alcohol **12h** as a colorless liquid in an almost quantitative yield. (Found: C, 65.6; H, 8.3; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%.) ν_{max} (neat) 3338, 3058, 3032, 2949, 2866, 1452, 1057, 869, 760 and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.92 (3H, m), 2.38 (1H, m), 2.5–3.3 (3H, m), 3.80 (5H, m), 3.83 4.07 (1H, dd, *J* 7.0, 11.6 Hz), 4.52 (1H, m), 7.32 (5H, m); δ_C ($CDCl_3$, +20 °C) 33.14, 37.23, 53.66, 59.70, 68.12, 72.15, 75.66, 128.15 (3C), 128.71 (2C), 138.10.

3.2.10. Cycloaddition of nitrone 7 with 4-penten-1-ol (11j). The crude mixture of cycloadducts was purified by chromatography over silica using 95:5 ether/methanol mixture as eluant to give non-separable mixture of isomers **12j** and **13j** as a colorless liquid (1.15 g, 92%). Spectral analysis of adducts revealed the presence of **12j** and **13j** in a ratio of 73:27, respectively, as determined by integration of several ^1H signals. One of the C(4)H of the major isomer **12j** appeared at δ 2.36 while the corresponding proton for the minor isomer **13j** appeared at 2.23 ppm. The following non-overlapping ^{13}C signals of the minor isomer **13j** were picked up from the spectrum of the adduct mixture and the known spectrum of **12j** (vide infra: Section 3.3.3); δ_C ($CDCl_3$, +20 °C) 29.29, 31.31, 33.52, 54.30, 62.28, 68.20, 74.16, 78.51, 128.01 (3C), 128.58 (2C), 138.16.

3.2.11. Cycloaddition of nitrone 7 with methyl methacrolein (14a), and conversion of 15a and 16a into 15d and 16d. Half of the crude mixture of cycloadducts was purified by chromatography over silica using 1:1 ether/hexane as eluant to give the hemiacetal **15a′** (200 mg, 34%) as colorless needles; mp 156.0–157.0 °C. (Found: C, 66.1; H, 7.3; N, 5.8. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95%.) ν_{max} (KBr) 3122, 2997, 2968, 2932, 2900, 2876, 2843, 1604, 1494, 1452, 1375, 1311, 1289, 1185, 1153, 1100, 1034, 996, 940, 878, 760 and 712 cm^{-1}; aldehyde absorption was not observed; δ_H ($CDCl_3$, +20 °C) 1.39 (3H, s), 1.86 (1H, ddd, *J* 2.8, 9.0, 12.0 Hz), 2.67 (1H, dt, *J* 12.4, 8.7 Hz), 3.06 (1H, d, *J* 4.3 Hz, OH, exchangeable), 3.27 (1H, ddd, *J* 2.90, 8.85, 11.4 Hz), 3.60 (1H, dt, *J* 11.1, 8.9 Hz), 3.80 (2H, m), 3.91 (1H, dd, *J* 5.2, 9.8 Hz), 4.69 (1H, d, *J* 4.3 Hz), and 7.30 (5H, m); on D_2O exchange the signal at δ 3.06 disappeared, while the signal at δ 4.69 collapsed into a singlet. The spectrum revealed the presence of a trace amount of an aldehyde by displaying a signal at δ 9.62 ppm. The spectra also revealed the presence of a minor hemiacetal by displaying a signal of the methyl proton as a singlet at δ 1.41 ppm. The ratio of the two hemiacetals was found to be 90:10, however, after D_2O exchange the ratio was changed to 64:36; δ_C ($CDCl_3$, +20 °C) 21.66, 32.38, 58.67, 68.06, 74.72, 89.46, 100.89, 126.97 (2C), 129.28, 128.44 (2C), 140.60. The ^{13}C signals for the minor hemiacetal were also observed. The non-overlapping signals of the minor hemiacetal were as follows: 1.41 (3H, s), 2.02 (1H, dd, *J* 8.1, 11.8 Hz), 2.55 (1H, m), 3.01 (1H, d *J* 7.05 Hz, OH exchangeable), 3.19 (1H, m), 3.45 (1H, m), 4.07 (2H, m), 4.37 (1H, dd, *J* 10.6, 13.4 Hz), 4.91 (1H, d, *J* 7.05 Hz).

Another half of the crude mixture of cycloadducts in methanol (3 cm^3) was reduced with $NaBH_4$ as before (Section 3.2.3) to give, after chromatographic purification, the

corresponding mixture of alcohol **15d** and **16d** as a colorless liquid (550 mg, 93%) in a ratio of 66:34, respectively, as determined by integration of the non-overlapping signals at δ 1.83 ppm (1H, major isomer) and δ 1.93 ppm (1H, minor isomer). The stereochemistry was confirmed by comparison to the spectrum of the pure alcohols **15d** and **16d** (vide infra: Section 3.2.12).

3.2.12. Cycloaddition of nitrone 7 with methyl methacrylate (14b), and conversion of 15b and 16b into 15d and 16d. The crude mixture of cycloadducts was purified by chromatography over silica using 1:1 ether/hexane as eluant to give the cycloadduct **16b** (117 mg, 9%). Continued elution afforded a mixture of **15b** and **16b** (57 mg, 4%), and finally the isomer **15b** (886 mg, 67%) as a colorless liquid. The total isolated yield for the addition reaction was thus found to be 80%. The diastereomeric ratio of **15b** and **16b** was found to be around 86:14, respectively.

Major isomer **15b**: (Found: C, 63.2; H, 7.2; N, 5.3. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%.) ν_{max} (neat) 3497, 2952, 2850, 1732, 1602, 1493, 1452, 1373, 1285, 1205, 1144, 983, 919, 848, 761 and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.52 (3H, s), 2.04 (1H, m), 2.73 (1H, m), 2.90 (1H, m and 1H OH), 3.50 (1H, m), 3.65 (1H, m), 3.80 (3H, s), 3.95 (1H, m), 4.18 (1H, m) and 7.30 (5H, m); ^{13}C spectrum is broad and complicated due to slow nitrogen inversion.

Minor isomer **16b**: (Found: C, 63.4; H, 7.1; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%.) ν_{max} (neat) 3494, 2953, 2847, 1737,1494, 1452, 1407, 1372, 1286, 1199, 1125, 1063, 979, 933, 842, 761 and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.55 (3H, s), 2.03 (1H, m), 2.50 (1H, m), 2.74 (1H, m), 2.93 (1H, m), 3.50 (1H, br, OH), 3.74 (1H, m), 3.81 (3H, s), 3.88 (1H, m), 3.99 (1H, m) and 7.30 (5H, m); δ_C ($CDCl_3$, −30 °C) 23.21, 38.47, 52.85, 53.43, 67.10, 71.67, 81.89, 127.92 (2C), 128.03, 128.48 (2C), 138.16, 175.87.

The above cycloaddition reaction was repeated at 0 and 25 °C for duration of 6 and 3 days, respectively, to give the adducts **15b** and **16b** in 53 and 87% yields. Integration of several proton signals in ^1H NMR spectrum in $CDCl_3$ indicated the ratio of the isomers.

The pure adducts **15b** and **16b** was reduced with lithium aluminum hydride as before (vide supra). The alcohols were purified by chromatography using CH_2Cl_2/methanol (97:3) as eluant to give **15d** (90 mg, 93%) and **16d** (40 mg, 90%) as colorless liquids. Compound **15d**: (Found: C, 65.6; H, 8.1; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%.) ν_{max} (neat) 3380, 3060, 3030, 2973, 2932, 2876, 1603, 1493, 1452, 1374, 1309, 1269, 1061, 893, 760, 735 and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.26 (3H, br s), 1.83 (1H, m), 2.40 (1H, m), 2.60–3.30 (4H, br), 3.52 (1H, m), 3.61 (1H, m), 3.71 (1H, m), 3.92 (1H, m), 4.09 (1H, m), 7.30 (5H, m); δ_C ($CDCl_3$, +20 °C) 23.99, 35.07, 54.04, 79.28, 68.71, 72.15, 85.00, 128.08 (3C), 128.63 (2C), 138.10. Compound **16d**: (Found: C, 65.7; H, 8.0; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%.) ν_{max} (neat) 3381, 3064, 3031, 2973, 2931, 2876, 1494, 1453, 1376, 1116, 1060, 889, 841, 760 and 703 cm^{-1}; δ_H($CDCl_3$, +20 °C) 1.32 (3H, s), 1.66 (1H, m), 1.93 (1H, m), 2.38 (1H, m), 2.56 (1H, m), 3.00 (2H, m), 3.20–3.80 (4H, br), 4.09 (1H, m), 7.30 (5H, m). δ_C ($CDCl_3$, +20 °C) 22.78, 35.76, 55.47, 68.35, 71.20, 74.43, 83.01, 127.88, 128.31 (2C), 128.77 (2C), 138.10.

3.2.13. Cycloaddition of nitrone 7 with *tert*-butyl methacrylate (14c). The crude mixture of cycloadducts was purified by chromatography over silica using using ether/hexane as eluant to give the non-separable adducts **15c** and **16c** as a colorless liquid in 85% yield. The ^1H NMR spectrum of the crude as well as the purified mixture revealed the presence of two isomers. The C(5)-Me methyl proton appeared as a singlet at δ 1.49 (major) and δ 1.50 (minor), while the *tert*-butyl proton appeared at δ 1.52 (major) and δ 1.53 (minor) in a ratio of 87:13, respectively. The major isomer was assigned to the stereochemistry as depicted in **15c** because of its similarity to the major adduct **15b** in their ^1H NMR spectral data. **15c/16c** mixture, colorless liquid. (Found: C, 66.3; H, 8.1; N, 4.5. $C_{17}H_{25}NO_4$ requires C, 66.43; H, 8.20; N, 4.56%.) ν_{max} (neat) 3466, 3062, 3030, 2978, 2935, 2876, 1728, 1454, 1369, 1290, 1143, 1063, 931, 846, 758 and 702 cm^{-1}. Major isomer **15c** displayed the following signals: δ_H ($CDCl_3$, +20 °C) 1.49 (3H, s), 1.52 (9H, s), 2.01 (1H, m), 2.68 (1H, m), 2.92 (2H, m), 3.73 (1H, dd, *J* 3.50, 11.45 Hz), 3.94 (1H, dd, *J* 5.05, 8.40 Hz), 4.18 (1H, dd, *J* 8.1, 11.45), 4.18 (1H, m) and 7.30 (5H, m). The adducts **15c** and **16c** were converted into the methyl methacrylate adducts **15b** and **16b** by ester exchange with methanol using procedure as described in Section 3.2.5.

3.2.14. Cycloaddition of nitrone 7 with methallyl alcohol (14d). The crude mixture of cycloadducts was purified by chromatography over silica using CH_2Cl_2/methanol (97:3) as eluant to give a non-separable mixture of alcohols **15d** and **16d** as a colorless liquid (973 mg, 82%) in a ratio of 67:33 as determined by integration of the C(5) methyl singlets. The ^1H NMR spectrum of the mixture of **15d** and **16d** was compared with that of the pure isomer **15d** (vide supra: Section 3.2.12).

3.2.15. Cycloaddition of nitrone 7 with *tert*-butyldimethylsilyl 2-methyl-2-propenyl ether (14e). The crude mixture of cycloadducts was separated by chromatography over silica using 9:1 hexane/ether as eluant to give **16e** (460 mg), followed by a mixture of **15e** and **16e** (243 mg) and finally, **15e** (597 mg). The isomers **15e** and **16e** (colorless liquid, 74%) were formed in a ratio of 58:42, respectively, as determined by proton NMR analyses of the crude as well as separated fractions.

Major isomer **15e**: (Found: C, 64.6; H, 9.4; N, 3.8. $C_{19}H_{33}NO_3Si$ requires C, 64.91; H, 9.46; N, 3.98%.) ν_{max} (neat); 3443, 3062, 3030, 2954, 2930, 2857, 1493, 1462, 1411, 1390, 1362, 1310, 1255, 1102, 938, 897, 838, 778 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.10 (6H, s), 0.93 (9H, s), 1.30 (3H, s), 1.83 (1H, m), 2.22 (1H, m), 2.69 (1H, m), 2.99 (1H, m), 3.56 (2H, AB, *J* 10.1 Hz), 3.70 (1H, m), 3.83 (1H, m), 4.06 (1H, dd, *J* 7.5, 11.5 Hz), 7.30 (5H, m); δ_C ($CDCl_3$, +20 °C) (−)5.49, (−)5.39, 18.25, 23.90, 25.84 (3C), 36.10, 54.04, 68.00, 68.45, 73.18, 83.90, 127.90 (2C), 128.11, 128.52 (2C), 138.49.

Minor isomer **16e**: (Found: C, 64.7; H, 9.3; N, 4.0. $C_{19}H_{33}NO_3Si$ requires C, 64.91; H, 9.46; N, 3.98%.) ν_{max} (neat); 3440, 3063, 3030, 2958, 2930, 2857, 1493, 1460, 1410, 1391, 1363, 1311, 1254, 1101, 938, 899, 838, 777 and 701 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.35 (3H, s), 1.84 (1H, m), 2.05 (1H, m), 2.45-3.10 (3H, m), 3.38-3.85 (4H, m), 4.04 (1H, dd, *J* 7.7, 11.4 Hz), 7.30 (5H, m); δ_C ($CDCl_3$, +20 °C) (−)5.46 (2C), 18.22, 23.56, 25.64 (3C), 36.48, 54.42, 68.24, 69.14, 73.72, 83.16, 127.98 (3C), 128.55 (2C), 138.46.

The cycloadducts **15e** and **16e** were hydrolyzed in methanolic HCl as before (Section 3.2.7) to obtain the alcohols **15d** and **16d,** respectively, in an almost quantitative yield.

3.2.16. Cycloaddition of nitrone 7 with dimethyl methylenemalonate (14f). The crude cycloadduct was purified by chromatography over silica using ether/hexane as eluant to give adduct **15f** as a colorless liquid (1.39 g, 90%). (Found: C, 58.2; H, 6.2; N, 4.4. $C_{15}H_{19}NO_6$ requires C, 58.25; H, 6.19; N, 4.53%.) ν_{max} (neat) 3491, 3030,2956, 2885, 1746, 1453, 1436, 1285, 1204, 1110, 761 and 704 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.70–3.20 (4H, br m), 3.70–4.20 (4H br m, including OH), 3.83 (3H, s), 3.84 (3H, s), 7.30 (5H, m); δ_C ($CDCl_3$, +20 °C) 36.24, 53.33, 53.46, 66.93, 72.30, 85.37, 91.18, 128.28, 128.69 (2C), 128.93 (2C), 138.18, 168.60, 169.14.

3.2.17. Cycloaddition the nitrone 9 with 1-hexene (11a). The crude mixture of cycloadducts was purified by chromatography over silica using 1:4 ether/hexane as eluant to give a non-separable mixtures of the cycloadducts **18** and **19** (1.11 g, 79%) as a colorless liquid in a ratio of 95:5 as determined by the peak heights of major and minor methyl singlets of the camphor moiety. (Found: C, 72.4; H, 11.0; N, 4.8. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.10; N, 4.98%.) ν_{max} (neat) 3344, 2955, 2929, 2876, 1460, 1386, 1370, 1289, 1120, 1096, 1073 and 1005 cm^{-1}; ($CDCl_3$, +20 °C) 0.78 (3H, s), 0.89 (3H, t, *J* 7.0 Hz), 0.97 (3H, s), 1.17 (3H, s), 1.00–1.78 (11H, m), 1.91 (1H, m), 2.34 (1H, m), 2.66 (1H, m), 2.76 (1H, m), 3.29 (1H, m), 3.59 (1H, m), 3.64 (1H, m), 4.10 (1H, m). Methyl singlet for the minor isomer was observed at 0.82, 0.99 and 1.09 ppm. The peak height of these signals was used to calculate the ratio of isomers as 95:5; δ_C ($CDCl_3$, 20 °C) 11.32, 13.99, 21.20, 21.67, 22.56, 27.24, 28.44, 33.00, 34.63, 35.76, 46.74, 49.12, 49.97, 53.62, 74.38, 76.89, 80.65.

3.2.18. Cycloaddition of nitrone 9 with styrene (11b). The crude mixture of cycloadducts was purified by chromatography over silica using 1:4 ether/hexane as eluant to give a non-separable mixture of the cycloadducts **20** and **21** (1.22 g, 81%) as a colorless liquid. Major and minor isomer were found in a ratio of 96:4 as determined by integration of C5(H) signal of **20** appearing at δ 5.13 (major) and that of **21** at δ 5.01 (minor). (Found: C, 75.5; H, 8.9; N, 4.6. $C_{19}H_{27}NO_2$ requires C, 75.71; H, 9.03; N, 4.65%.) ν_{max} (neat) 3536, 3062, 3028, 2951, 1604, 1492, 1454, 1391, 1368, 1291, 1242, 1216, 1120, 1099, 1067, 1025, 990, 974, 943, 809, 760, and 700 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.78 (3H, s), 0.97 (3H, s), 1.06 (2H, m), 1.20 (3H,s), 1.47 (1H, m), 1.75 (2H, m), 2.36 (1H, m), 2.74 (1H, m), 2.90 (2H, m), 3.49 (2H, m), 3.67 (1H, m), 5.14 (1H, m), 7.31 (5H, m); δ_C ($CDCl_3$, −30 °C) 11.4, 21.1, 21.3, 27.2, 32.6, 37.9, 46.7, 49.0, 49.6, 54.2, 74.3, 78.2, 80.3, 125.8 (2C), 127.4, 128.5 (2C), 143.1.

3.2.19. Cycloaddition of nitrone 9 with methyl acrylate (11d). The crude mixture of cycloadducts was purified by chromatography over silica using 1:4 ether/hexane as eluant to afford the major and minor cycloadducts **22** and **23** (1.20 g, 85%) as a non-separable mixture of isomers. Crystallizations from hexane/ether afforded the major cycloadduct **22** as colorless needles. The diastereomeric ratio of **22** and **23** was found to be around 65:35, respectively. The stereochemistry of the major isomer **22** was assigned by X-ray diffraction analysis.

Major isomer **22**: mp 78–78.5 °C (hexane/ether). (Found: C, 63.7; H, 8.9; N, 4.8. $C_{15}H_{25}NO_4$ requires C, 63.58; H, 8.89; N, 4.94%.) ν_{max} (KBr) 3506, 2952, 1742, 1444, 1362, 1221, 1080, and 813 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.78 (3H, s), 0.99 (3H, s), 1.07 (2H, m), 1.11 (3H, s), 1.46 (1H, m), 1.72 (2H, m), 2.51 (1H, m), 2.61 (1H, m), 2.83 (2H, d, *J* 6.7 Hz), 3.32 (1H, m), 3.71 (1H, d, *J* 6.4 Hz), 3.76 (3H, s), 4.04 (1H, OH), 4.56 (1H, m); δ_C ($CDCl_3$, −30 °C) 11.4, 21.0, 21.5, 27.3, 32.5, 32.7, 46.7, 49.2, 49.9, 52.3, 52.7, 73.67, 73.73, 80.4, 173.7. The following ^1H NMR signals for the minor isomer **23** was extracted from the spectrum of the mother liquor, which was rich in the minor isomer **23**: 0.78 (3H, s), 0.96 (3H, s), 1.12 (3H, s), 3.74 (3H, s), 4.53 (1H, m).

3.2.20. Cycloaddition of nitrone 9 with methyl methacrylate (14b). The crude mixture of cycloadducts was purified by chromatography over silica using 1:4 ether/hexane as eluant to give the mixture of minor isomer **25** (346 mg, 23%) contaminated with a small percentage of major isomer. Continued elution afforded the major isomer **24** (959 mg, 65%) contaminated by a minor portion of minor isomer. Repeated chromatography was unable to separate the two isomers since they have very close R_f values. The diastereomeric ratio of **24** and **25** was found to be around 66:34, respectively, as determined by integration of several methyl proton signals in ^1H NMR spectrum of the crude reaction mixture.

Major isomer **24**: (Found: C, 64.4; H, 9.2; N, 4.7. $C_{16}H_{27}NO_4$ requires C, 64.62; H, 9.15; N, 4.71%.) ν_{max} (neat) 3547, 2952, 1736, 1458, 1391, 1369, 1291, 1201, 1121, 1074, 984, 828, and 750 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.78 (3H, s), 0.96 (3H, s), 1.17 (3H, s), 1.46 (1H, m), 1.53 (3H, s), 1.60 (2H, m), 1.70 (2H, m), 2.22 (1H, m), 2.82 (3H, m), 3.31 (2H, m), 3.67 (1H, m), 3.75 (3H, s).

Minor isomer **25**: (Found: C, 64.5; H, 9.1; N, 4.8. $C_{16}H_{27}NO_4$ requires C, 64.62; H, 9.15; N, 4.71%.) ν_{max} (neat) 3540, 2953, 2876, 1745, 1479, 1454, 1392, 1370, 1355, 1289, 1201, 1098, 985, 963, 829, and 753 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.76 (3H, s), 0.98 (3H, s), 1.05 (2H, m), 1.09 (3H, s), 1.30 (1H, m), 1.49 (3H, s), 1.68 (2H, m), 2.08 (1H, ddd, *J* 1.9, 9.0, 11.0 Hz), 2.60 (1H, app q, *J* 8.9 Hz), 2.81 (2H, m), 3.28 (1H, t, *J* 8.1), 3.72 (1H, d, *J* 6.4 Hz), 3.75 (3H, s).

3.2.21. Cycloaddition of nitrone 9 with dimethyl methylenemalonate (14f). The crude cycloadduct was purified by chromatography over silica using ether/hexane as eluant to

give adduct **26** as colorless crystals (79%); mp 131–132.0 °C (ether). (Found: C, 59.7; H, 8.0; N, 4.0. $C_{17}H_{27}NO_6$ requires C, 59.81; H, 7.97; N, 4.10%.) ν_{max} (KBr) 3515, 2958, 2881, 1753, 1440, 1290, 1270, 1216, 1095, 1003, 926, 828, and 771 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 0.77 (3H, s), 0.97 (3H, s), 1.07 (2H, m), 1.10 (3H, s), 1.45 (1H, m), 1.70 (2H, m), 2.70 (1H, m), 2.86 (2H, m), 2.94 (1H, m), 3.37 (1H, m), 3.67 (1H, m), 3.74 (1H, m), 3.79 (3H, s), 3.81 (3H, s); δ_C ($CDCl_3$, 20 °C) 11.36, 21.11, 21.54, 27.39, 32.90, 36.90, 46.93, 49.30, 50.39, 53.26, 53.45, 53.51, 74.51, 80.63, 84.42, 167.15, 170.19.

3.3. Cycloaddition of nitrone 7 in the presence of $MgBr_2$

3.3.1. Cycloaddition of nitrone 7 with 1-hexene (11a). To a solution of hydroxylamine **10** (153 mg, 1.0 mmol) in dichloromethane (20 cm^3), was added paraformaldehyde (34 mg, 1.13 mmol) and the mixture was stirred in a closed vessel under N_2 at 65 °C for 2 h. Thereafter, the solution was cooled to room temperature and the volume of the solution was reduced to 5 cm^3 by gently blowing N_2 at 40 °C. This process is expected to remove moisture (H_2O) by evaporation along with CH_2Cl_2. Then $MgBr_2$ (184 mg, 1.0 mmol) was added to the solution. The resulting suspension was stirred at 20 °C for 15 min after, which 1-hexene (4.0 mmol) was added. The reaction mixture was then stirred at 65 °C in the closed vessel under N_2 for 48 h. During the reaction, a precipitate of magnesium salts was observed. After the elapsed time, the reaction mixture was cooled to room temperature and was taken up in 10% K_2CO_3 (20 cm^3) and extracted with CH_2Cl_2 (3×20 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using ether/hexane mixture as eluant to give a non-separable mixture of isomers **12a** and **13a** as a colorless liquid (192 mg, 77%). The ratio of **12a** and **13a** was found to be 85:15, respectively, as determined by ^1H NMR spectroscopic analysis (vide supra).

3.3.2. Cycloaddition of nitrone 7 with 3-buten-1-ol (11h). As described in Section 3.3.1, the addition reaction was carried out using hydroxylamine **10** (307 mg, 2.0 mmol) and 3-buten-1-ol (2.0 mmol) in the presence of 1 equiv of $MgBr_2$ at 65 °C for 48 h. After usual work up the residual liquid was purified by chromatography over silica using 95:5 ether/methanol as eluant to give a non-separable mixture of isomers **12h** and **13h** as a colorless liquid (430 mg, 91%). The ratio of **12h** and **13h** was found to be 89:11, respectively, determined by ^1H NMR spectroscopic analysis as before (Section 3.2.9).

3.3.3. Cycloaddition of nitrone 7 with 4-penten-1-ol (11j). As described in Section 3.3.1, the addition reaction was carried out using hydroxylamine **10** (230 mg, 1.5 mmol) and 4-penten-1-ol (1.5 mmol) in the presence of 1 equiv of $MgBr_2$ at 67 °C for 48 h. After usual work up the residual liquid was purified by chromatography over silica using 97:3 dichloromethane/methanol as eluant to give a non-separable mixture of isomers **12j** and **13j** as a colorless liquid (350 mg, 93%). The ratio of **12j** and **13j** was found to be 91:9, respectively, determined by ^1H NMR spectroscopic analysis as before. (Found: C, 66.7; H, 8.3; N, 5.4. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57%.) ν_{max} (neat) 3380, 3060, 2941, 2871, 1493, 1452, 1376, 1357, 1328, 1275, 1177, 1060, 943, 851, 759, 734 and 702 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 1.60–190 (5H, m), 2.35 (1H, m), 2.74 (1H, m), 2.99 (1H, m), 3.70 (3H, m), 3.83 (1H, dd, *J* 3.4, 7.4 Hz), 4.06 (1H, dd, *J* 7.1, 11.4 Hz), 4.34 (1H, m), 7.30 (5H, m), the 2H for OHs are spread out in the range 2–3.5 ppm; δ_C ($CDCl_3$, +20 °C) 29.29, 31.31, 33.52, 53.31, 62.36, 68.20, 71.45, 77.30, 128.01 (3C), 128.58 (2C), 138.16.

3.3.4. Cycloaddition of nitrone 7 with methylallyl alcohol (14d). As described in Section 3.3.1, the addition reaction was carried out using hydroxylamine **10** (1.0 mmol) and methylallyl alcohol (1.1 mmol) in the presence of 1 equiv of $MgBr_2$ at 65 °C for 24 h. After usual work up, the residual liquid was purified by silica gel chromatography using CH_2Cl_2/MeOH (95:5) as eluant to give a non-separable mixture of alcohols **15d** and **16d** as a colorless liquid (95%). The ^1H NMR spectrum revealed the presence of **15d** and **16d** in a ratio of 97:3, respectively. The ratio was determined by integration of the C(5)-methyl singlets as before (Section 3.2.12).

3.4. Conversion of adduct 15f into its acrylate ester 27

To a solution of the adduct **15f** (1.00 g, 3.23 mmol) and pyridine (10 mmol) in CH_2Cl_2 (passed through Al_2O_3) (100 cm^3) under N_2 was added drop wise (ca. 2 min) acrolyl chloride (6 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 1 h. TLC experiment (silica, hexane/ether) was carried out to determine the completion of reaction. (If incomplete, a further amount of acrolyl chloride/pyridine has to be added.) The reaction mixture was washed with aqueous $NaHCO_3$ (20 cm^3). The aqueous layer was reextracted with dichloromethane (2×25 cm^3). The combined organic layers was dried, concentrated, and purified by chromatography using 4:1 hexane/ether mixture as the eluant to give the ester **27** (926 mg, 79%) as a colorless liquid. (Found: C, 59.3; H, 5.9; N, 3.8. $C_{18}H_{21}NO_7$ requires C, 59.50; H, 5.83; N, 3.85%.) ν_{max} (neat) 3032, 3004, 2955, 2849, 1745, 1720, 1634, 1494, 1454, 1435, 1407, 1284, 1192, 1105, 991, 918, 810, 761, and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.60–3.10 (4H, m), 3.80 (3H, s), 3.83 (3H, s), 4.08 (1H, app t, *J* 6.0 Hz), 4.50 (1H, dd, *J* 7.0, 11.0 Hz), 4.74 (1H, m), 5.73 (1H, d, *J* 10.4 Hz), 6.01 (1H, dd, *J* 10.4, 17.3 Hz), 6.26 (1H, d, *J* 17.3 Hz), 7.30 (5H, m).

3.5. Cycloreversion of acrylate ester 27 to alkenenitrone 28, and its intramolecular cycloaddition to 29. Conversion of 29 into 13d

A solution of acrylate ester **27** (500 mg, 1.38 mmol) in anhydrous toluene (400 cm^3) was heated to 120 °C in a closed vessel for 30 h. After removal of the toluene by distillation using a 25 cm Vigreux column, the residual liquid was chromatographed over silica using a 2:1 hexane/ether to give the intramolecular cycloaddition product **29** as colorless crystals (127 mg, 42%); mp 157–158 °C (CH_2Cl_2/ether). (Found: C, 65.6; H, 5.9; N, 6.4. $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39%.) ν_{max} (KBr) 3059, 2992, 2960, 2886, 1728, 1460, 1404, 1334, 1262, 1239, 1181, 1086, 1047, 1014, 900, 791, 754 and 703 cm^{-1}; δ_H ($CDCl_3$, +20 °C) 2.68 (1H, m), 2.92 (1H, m), 3.16 (1H, m), 3.25 (1H, m), 3.98 (1H, d, *J* 12.2 Hz), 4.08 (1H, d, *J* 9.5 Hz), 5.05 (1H, d, *J* 9.8 Hz), 5.07 (1H, dd, *J* 6.5, 9.8 Hz), 7.35 (5H, m); δ_C ($CDCl_3$,

+20 °C) 34.60, 55.44, 70.88, 73.69, 79.63, 127.65 (2C), 128.62, 128.91 (2C), 137.43, 172.54.

The adduct **29** (20 mg) on treatment with 5:1 methanol/HCl (1 cm^3) at 20 °C for overnight, followed by work up as described before (Section 3.2.5) afforded the adduct **13d** in almost quantitative yield.

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